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<b>(21) International Application Number:</b> PCT/US97/12561 <b>(22) International Filing Date:</b> 24 July 1997 (24.07.97) <b>(30) Priority Data:</b> 60/022,564      24 July 1996 (24.07.96)      US <b>(71) Applicant:</b> BIOSYTES USA, INC. [US/US]; P.O. Box 261, Tenaflly, NJ 07670 (US). <b>(72) Inventor:</b> GOLDMAN, Robert; 138 Lexington Avenue, Cresskill, NJ 07626 (US). <b>(74) Agent:</b> AUFRICHTIG, Peter, D.; Aufrichtig Stein & Aufrichtig, P.C., 300 East 42nd Street, New York, NY 10017 (US).		<b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> METHOD FOR ENHANCING DISSOLUTION PROPERTIES OF RELATIVELY INSOLUBLE DIETARY SUPPLEMENTS AND PRODUCT INCORPORATING SAME		
<b>(57) Abstract</b> <p>A method for enhancing the dissolution properties of relatively insoluble dietary supplements is provided in accordance with the invention. The method includes the steps of providing at least one relatively water-insoluble dietary supplement, solubilizing the dietary supplement with a solubilizer, and incorporating an edible polyhydric alcohol into the solubilized dietary supplement to provide a liquid dietary supplement composition that will dissolve spontaneously in the gastrointestinal tract with the minimum agitation which normally occurs there due to peristaltic action. The liquid dietary supplement composition can be readily supplied by incorporation in a gelatin capsule and a gelatin capsule having a liquid dietary supplement incorporated therein is also provided in accordance with the invention. The gelatin capsule dissolves readily in the digestive tract and the dietary supplement has enhanced bioavailability in comparison to prior art gelatin capsules.</p>		

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## METHOD FOR ENHANCING DISSOLUTION PROPERTIES OF RELATIVELY INSOLUBLE DIETARY SUPPLEMENTS AND PRODUCT INCORPORATING SAME

### Field of the Invention

This invention relates generally to relatively water insoluble dietary supplements and, in particular, to a method for enhancing the dissolution properties of such relatively water insoluble dietary supplements and to a dietary supplement product having enhanced dissolution properties so that solution will take place spontaneously with the minimum agitation which normally occurs due to peristaltic action in the gastrointestinal tract.

### Background of the Invention

The use of dietary supplements is well known. For example, coenzyme Q-10 is a vitamin-like substance used around the world to treat congestive heart failure and other cardiac problems. In many countries, St. John's wort is widely recognized as useful for relieving depression as effectively as many antidepressant pharmaceuticals, but without unpleasant side effects. The list of such supplements is virtually endless.

One of the difficulties encountered in formulated such supplements for human ingestion is that many of the supplements are relatively water insoluble. Since the human digestive tract is a substantially aqueous system, it is difficult to provide these supplements in forms that will dissolve readily in the digestive tract and be available for use, i.e. bioavailable.

U.S. Patent No. 4,572,915 issued to Crooks on February 25, 1986 discloses aqueous formulations for fat soluble vitamins, essential nutrients, herb oils, and pharmaceutical agents. The formulations are prepared by first admixing the fat soluble vitamin, essential nutrient, or agent with a suitable amount of polyethoxylated castor oil and a pharmaceutically acceptable polyol, such as glycerol, to provide a non-aqueous

phase. Thereafter, an aqueous phase containing mostly water and optionally a preservative, such as sodium benzoate, is slowly added to the agitated non-aqueous phase at an elevated temperature. The admixture is cooled and provided as a clear, homogeneous, micellized aqueous formulation.

It is often desirable to provide relatively water insoluble dietary supplements in a gelatin capsule form. Gelatin capsules, which can be hard or soft, are considered to be tasteless and easy to swallow. Furthermore, they dissolve readily in the digestive tract. Such capsules are filled with compositions that are provided to the digestive tract upon dissolution of the capsule.

One difficulty of using gelatin capsules arises because such capsules can not contain aqueous liquid compositions of the type disclosed in the Crooks patent. However, when non-aqueous compositions of relatively water insoluble dietary supplements are provided, the dietary supplement may not become bioavailable upon dissolution of the gelatin capsule.

It would, therefor, be desirable to provide a gelatin capsule containing a liquid composition of a relatively water insoluble dietary supplement that provides for enhanced bioavailability of the dietary supplement.

A goal of the invention is to provide a method for enhancing the dissolution properties of relatively water insoluble dietary supplements.

Another goal of the invention is to provide a dietary supplement product having improved dissolution properties.

A further goal of the invention is to provide a dietary supplement in the form of a gelatin capsule wherein the liquid dietary supplement contained therein has increased bioavailability.

Still other objects and advantages of the invention will in part be obvious and will in part be apparent from the specification.

### Summary of the Invention

Generally speaking, a method for enhancing the dissolution properties of relatively insoluble dietary supplements is provided in accordance with the invention. The method includes the steps of providing at least one relatively water insoluble dietary supplement, solubilizing the dietary supplement with a solubilizer, and incorporating an edible polyhydric alcohol into the solubilized dietary supplement to provide a liquid dietary supplement composition that can be dissolved in an aqueous system. The liquid dietary supplement composition can be readily supplied by incorporation in a gelatin capsule.

A gelatin capsule having a liquid dietary supplement incorporated therein is also provided in accordance with the invention. The gelatin capsule dissolves readily in the digestive tract and the dietary supplement has enhanced bioavailability in comparison to prior art gelatin capsules.

The invention accordingly comprises the several steps and the relation of one or more of such steps with respect to each of the others, and the composition possessing the features, properties, and the relation of constituents, which are exemplified in the following detailed disclosure, and the scope of the invention will be indicated in the claims.

### Brief Description of the Drawings

For a fuller understanding of the invention, reference is had to the following description taken in connection with the accompanying drawings, in which:

FIG. 1 is a graph showing Mean Plasma Coenzyme Q-10 Values During Supplementation for a reference control and a Coenzyme Q-10 product prepared in accordance with the invention;

Fig. 2 is a graph showing Mean Plasma Coenzyme Q-10 AUC Following Supplementation for a reference and a Coenzyme Q-10 product prepared in accordance with the invention; and,

FIG. 3 is a graph showing Percentage Comparison of 28-Day AUC for a reference and a Coenzyme Q-10 product prepared in accordance with the invention.

#### Detailed Description of the Preferred Embodiments

The invention includes a method for enhancing the dissolution properties of relatively insoluble dietary supplements or therapeutic agents. The method includes the steps of providing at least one relatively water insoluble dietary supplement, solubilizing the dietary supplement with a solubilizer, and incorporating an edible polyhydric alcohol into the solubilized dietary supplement to provide a liquid dietary supplement composition that can be dissolved in an aqueous system. The liquid dietary supplement composition can be readily supplied by incorporation into a gelatin capsule or absorption onto a starch.

The dietary supplements or therapeutic agents that may be used in accordance with the invention is a virtually limitless list. In general, such therapeutic agents are relatively insoluble in water and the method provided enhances the dissolution properties of such agents so that they become soluble in the substantially aqueous system of the human digestive tract and solution will take place spontaneously with the minimum agitation which normally occurs due to peristaltic action in the gastrointestinal tract.

Suitable dietary supplements or therapeutic agents include, for example, micronutrients such as vitamins, minerals, and other nutritional co-factors. Exemplary agents include, but are not limited to, Coenzyme Q-10 (Ubiquinone), Tumeric Extract (Curcuminoids), Beta Carotene, Mixed Carotenoids Complex, Lutein, Lycopene, Tocotrienols, Tocopherols (Vitamin E), Saw Palmetto Lipid Extract, Echinacea Extract, Hawthorne Berry Extract, Ginseng Extract, Lipoic Acid (Thiolic Acid), Ascorbyl Palmitate, Kava Extract, St. John's Wort (Hypericum), Extract of Quercetin, Dihydrocypandrosterone, Indol-3-carbinol, and mixtures thereof.

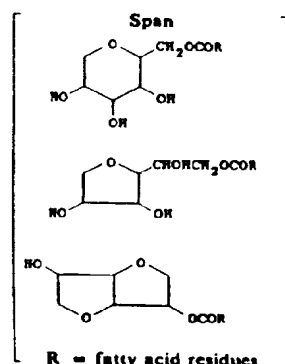
In particular, it is often advantageous to use combinations of therapeutic agents. For example, St. John's Wort and Kava Extract are believed to be useful for relief of depression and as a tranquilizing agent, respectively. Since the kavalactones, which are the active principals of the Kava Extract, and the hypericum, which is the active component of St. John's Wort, are all water insoluble, the method provided in accordance with the invention can be used to simultaneously solubilize all of the active components. Other combinations are also possible and desirable.

The dietary supplement or therapeutic agent is used in an amount between about 1 and 50% by weight of the solubilized composition, preferably in an amount between about 1 and 25% by weight, and more preferably in an amount between about 5 and 10%. When a mixture of therapeutic agents are used, the total amounts are within these ranges including combinations of both water soluble and water insoluble compounds with water insoluble compounds such as Ginko Biloba Extract and the Proanthocyanidines found in the extracts of Grape Seed and the bark of the French Maritime Pine.

The method provided in accordance with the invention requires that the

dietary supplement or therapeutic agent be solubilized or dissolved in a solubilizer or surfactant. Such solubilizers are generally non-ionic surface active agents and must be generally recognized as safe (G.R.A.S.). The solubilizers may be complex esters or esters prepared from hexahydric alcohols, alkylene oxides, and fatty acids. Suitable solubilizers include Span type materials and Tween or Polysorbate type materials, which are known for use as emulsifiers, stabilizers, and thickeners in foods, cosmetics, and medicinal products.

In particular, Span type materials are partial esters of the common fatty acids, namely, lauric acid, palmitic acid, stearic acid, and oleic acids, and hexitol anhydrides, namely, hexitans and hexides, derived from sorbitol. In general, such sorbitan fatty acid esters have the structure:



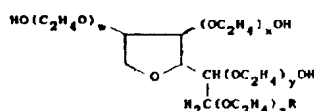
when R is  $\text{OOC}(\text{C}_{11}\text{H}_{23})$  the structure represents sorbitan laurate (Span 20); when R is  $\text{OOC}(\text{C}_{17}\text{H}_{35})$  the structure represents sorbitan stearate (Span 60); and when R is  $\text{OOC}(\text{C}_{17}\text{H}_{33})$  the structure represents sorbitan oleate (Span 80).

The hydrophilic character of the Span type materials is supplied by free hydroxyl and oxyethylene groups, while the lipophilic portion is found in the long chain fatty acids. These materials tend to be oil soluble and dispersible or insoluble in water. In a preferred embodiment of the present invention, at least a portion of the solubilizer



is sorbitan monooleate.

The Tween or Polysorbate type materials are oleate esters of sorbitol and its anhydrides copolymerized with about 20 moles of ethylene oxide per mole of sorbitol and sorbitol anhydride. The Tween or Polysorbate type materials are derived from the Span type materials by adding polyoxyethylene chains to the nonesterified hydroxyls. The Tween type products are soluble or well dispersible in water. These oleate esters have the structure:



In a preferred embodiment, the Tween type material is a sorbitan mono-9-octadecenoate poly(oxy-1,2-ethanediyl) derivative wherein the sum of w, x, y, and z is 20 (Tween 80 or Polysorbate 80).

The solubilizer is used in an amount between about 20 and 90% by weight of the solubilized composition, preferably in an amount between about 35 and 80% by weight, more preferably in an amount between about 50 and 75%. In an especially preferred embodiment, the solubilizer is a mixture of a Span type material and a Tween type material. The ratio of Span type material: Tween type material can range between about 1 and 2 parts Span type material to between about 20 and 30 parts Tween type material, preferably about 1 part Span type material to about 9 parts Tween type material. Since Span type materials are generally oil soluble and dispersible or insoluble in water and Tween type materials are generally soluble or well dispersible in water,

adjustment of ratio of the Span type materials to Tween type materials is effective for obtaining an appropriate degree of water solubility or insolubility of the solubilized composition, i.e. hydrophilic versus lipophilic properties.

The solubilized composition further includes an edible polyhydric alcohol. This component serves the important function of avoiding the necessity of slowly adding water to form an aqueous phase. In the absence of a polyhydric alcohol, a composition including a Span and/or Tween type emulsifier with a therapeutic agent therein would leave a firm gel upon dissolution of a gelatin capsule in which it could be contained. Such a firm gel would dissolve too slowly in the aqueous fluid of the digestive tract to be of any significant therapeutic benefit.

The edible polyhydric alcohol is preferably selected from the group consisting of propylene glycol, glycerol, and mixtures thereof. Edible propylene glycol has the structure 1,2-propanediol. Glycerol has the structure 1,2,3-propanetriol and is also known as glycerin.

The polyhydric alcohol is used in an amount between about 2 and 50% by weight of the solubilized composition, preferably between about 2 and 25% by weight, more preferably between about 4 and 20%.

The solubilized composition can readily be prepared by mixing the emulsifier and the polyhydric alcohol together. The mixture can be warmed to between about 50° and 60°C and the therapeutic agent can be added.

The solubilized composition does not contain water and is, therefore, suitable for use in gelatin capsules, which can be prepared by conventional means. In particular, soft gelatin capsules generally contain liquid compositions, although even two-piece hard gelatin capsules may be used. The gelatin capsules are tasteless, easy to

swallow and dissolve readily in the digestive tract. Once dissolved, the solubilized therapeutic agent spontaneously dissolves in the digestive fluids of the body with the minimal, slow agitation that occurs there. Alternatively, the solubilized composition may be absorbed onto a starch material and compressed to form tablets.

The following non-limiting Examples are presented for purposes of illustration only and are not to be construed in a limiting sense.

#### Example 1

Six hundred and twenty-five grams (625g) of Tween® 80, 125g of Span® 80, and 150g propylene glycol were mixed together and heated to between about 70° and 80°C. One hundred grams (100g) of Curcumin (Tumeric Extract) was added with continued stirring until a clear solution resulted. The solubilized Curcumin composition was cooled to room temperature and filled into 1,000 soft gelatin capsules in an amount of 1,000mg per capsule.

#### Example 2

Four hundred and thirty-two grams (432g) of Tween® 80, 85g of Span® 80, and 100g of glycerin were mixed together until a uniform solution resulted. The solution was warmed to between about 50° and 60°C. Fifty grams (50g) of Kava extract containing 50% kavalactones was added and stirred until dissolution occurred. Three hundred and thirty-three grams (333g) of St. John's Wort Extract containing 0.3% hypericum was added and stirred until a uniform suspension resulted. Although the hypericum, which is the active component of the St. John's Wort Extract dissolved in the solution, other inert components did not dissolve. The solubilized Kava extract and St. John's Wort Extract was filled into 1,000 soft gelatin capsules containing 25mg of kavalactones and 1mg of hypericum per capsule.

### Example 3

One hundred and fifty-five grams (155g) of Tween® 60, 30g of Span® 80, and 40g of propylene glycol were mixed together and warmed to between about 40° and 50°C. Twenty-five grams (25g) of Indole-3-carbinol was added and stirred until a clear solution resulted. The solubilized Indole-3-carbinole composition was used to fill 1,000 soft gelatin capsules at 250mg of Indole-3-carbinole per capsule.

### Example 4

A Coenzyme Q-10 composition was prepared from 5.60% by weight of the solubilized composition of Span®80, 83.93% by weight of Tween® 80, 3.92%propylene glycol, and 3.55% Coenzyme Q-10. The solubilized Coenzyme Q-10 composition was incorporated into soft gelatin capsules. Testing of the capsules by the USP Dissolution method showed 100% dissolution of Coenzyme Q-10.

Each of the compositions prepared in accordance with Examples 1 - 4, inclusive, included a relatively water insoluble therapeutic agent in a solubilized form suitable for incorporation into a gelatin capsule. In preparing compositions of therapeutic agents, it is important to remember that the amount of active ingredients in any particular extract may have normal variations. Accordingly, it is often necessary to adjust the quantity of the extract used and the fill weight for each capsule in order to standardize the amount of active ingredient present in the capsule.

The solubilized compositions prepared in accordance with the invention result in greater bioavailability of the therapeutic agents when formulated in a gelatin capsule. Furthermore, since the therapeutic agent in each capsule is more bioavailable, the capsules can be prepared using smaller amounts of expensive therapeutic agents than prior art compositions. Plasma level studies have confirmed this observation.

Twenty-four (24) healthy volunteers were randomly assigned into two (2) groups. Each group contained three (3) white males, three (3) white females, three (3) black males, and three (3) black females. None of the volunteers had used Coenzyme Q-10 supplements prior to the study.

A first formulation of Reference Coenzyme Q-10 capsules was given to the first group of volunteers on a daily basis. The Reference Coenzyme Q-10 capsules contained Coenzyme Q-10 in a standard vegetable oil formulation.

A second formulation of Coenzyme Q-10 capsules prepared in accordance with Example 4 hereinabove (Q-Gel) was given to the second group of volunteers on a daily basis. The formulations of Coenzyme Q-10 were standardized to insure that each group of volunteers was receiving the same amount of Coenzyme Q-10.

The plasma Coenzyme Q-10 values of each volunteer were measured at 0, 7, 14, 21, and 28 days during supplementation. The Mean Plasma Coenzyme Q-10 Values for each group are graphically depicted in FIG. 1. As can be seen, the volunteers receiving the second formulation of Coenzyme Q-10 (Q-Gel) prepared in accordance with Example 4 had significantly higher plasma values indicating that the Coenzyme Q-10 was significantly more bioavailable.

The Mean Plasma Coenzyme Q-10 Area Under Curve Following Supplementation for each group of volunteers is shown in FIG. 2 and The Percentage Comparison of 28-Day Area Under Curve Between Formulations is shown in FIG. 3. As can be seen, each of these means of assessment also reflected that the Coenzyme Q-10 obtained from the Q-Gel formulation was significantly more bioavailable than the Coenzyme Q-10 in the reference formulation.

It will thus be seen that the objects set forth above, among those made

apparent from the preceding description, are efficiently obtained and, since certain changes may be made in carrying out the above method and in the composition set forth without departing from the spirit and scope of the invention, it is intended that all matter contained in the above description and shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

It is also to be understood that the following claims are intended to cover all of the generic and specific features of the invention herein described and all statements of the scope of the invention which, as a matter of language, might be said to fall therebetween.

Particularly it is to be understood that in said claims, ingredients or compounds recited in the singular are intended to include compatible mixtures of such ingredients wherever the sense permits.

## WHAT IS CLAIMED IS:

1. A method for enhancing the dissolution properties of dietary supplements comprising:

providing at least one dietary supplement;

solubilizing the dietary supplement with a solubilizer; and,

incorporating an edible polyhydric alcohol into the solubilized dietary supplement composition to provide a solubilized dietary supplement composition having enhanced dissolution properties.

2. The method of claim 1 wherein the dietary supplement is relatively water insoluble.

3. The method of claim 1 wherein the dietary supplement includes at least one vitamin.

4. The method of claim 1 wherein the dietary supplement includes at least one mineral.

5. The method of claim 1 wherein the dietary supplement includes a member of the group consisting of Coenzyme Q-10 (Ubiquinone), Tumeric Extract (Curcuminoids), Beta Carotene, Mixed Carotenoids Complex, Lutein, Lycopene, Tocotrienols, Tocopherols (Vitamin E), Saw Palmetto Lipid Extract, Exhinacea Extract, Hawthorne Berry Extract, Ginseng Extract, Lipoic Acid (Thiotic Acid), Ascorbyl Palmitate, Kava Extract, St. John's Wort Extract (Hypericum), Extract of Quercitin, Dihydrocpiandrosterone, Indol-3-carbinol, and mixtures thereof.

6. The method of claim 1 wherein the dietary supplement is present in an amount between about 1 and 50% by weight of the solubilized composition having enhanced dissolution properties.

7. The method of claim 1 wherein the solubilizer is selected from the group consisting of Span type materials and Tween type materials.

8. The method of claim 1 wherein the solubilizer is present in an amount between about 2 and 90% by weight of the solubilized composition having enhanced dissolution properties.

9. The method of claim 1 wherein the edible polyhydric alcohol is selected from the group consisting of propylene glycol, glycerol, and mixtures thereof.

10. The method of claim 1 wherein the edible polyhydric alcohol is used in an amount between about 2 and 50% by weight of the solubilized composition having enhanced dissolution properties.

11. The method of claim 1 further comprising the step of incorporating the solubilized composition having enhanced dissolution properties into a gelatin capsule for ingestion.

12. A solubilized composition having enhanced dissolution properties comprising:

at least one dietary supplement;

at least one solubilizer for solubilizing the dietary supplement; and,

at least one edible polyhydric alcohol incorporated into the solubilized dietary supplement composition.

13. The composition of claim 12 wherein the dietary supplement is relatively water insoluble.

14. The composition of claim 12 wherein the dietary supplement includes at least one vitamin.

15. The composition of claim 12 wherein the dietary supplement includes



at least one mineral.

16. The composition of claim 12 wherein the dietary supplement includes a member of the group consisting of Coenzyme Q-10 (Ubiquinone), Tumeric Extract (Curcuminoids), Beta Carotene, Mixed Carotenoids Complex, Lutein, Lycopene, Tocotrienols, Tocopherols (Vitamin E), Saw Palmetto Lipid Extract, Echinacea Extract, Hawthorne Berry Extract, Ginseng Extract, Lipoic Acid (Thiolic Acid), Ascorbyl Palmitate, Kava Extract, St. John's Wort Extract (Hypericum), Extract of Quercetin, Dihydrocypandrosterone, Indol-3-carbinol, and mixtures thereof.

17. The composition of claim 12 wherein the dietary supplement is present in an amount between about 1 and 50% by weight of the composition.

18. The composition of claim 12 wherein the solubilizer is selected from the group consisting of Span type materials, Tween type materials, and mixtures thereof.

19. The composition of claim 12 wherein the solubilizer is present in an amount between about 2 and 90% by weight of the composition.

20. The composition of claim 12 wherein the edible polyhydric alcohol is selected from the group consisting of propylene glycol, glycerol, and mixtures thereof.

21. The composition of claim 12 incorporated into a gelatin capsule.

22. The composition of claim 12 incorporated into a soft gelatin capsule.

23. The composition of claim 12 absorbed onto a starch and compressed into a tablet.

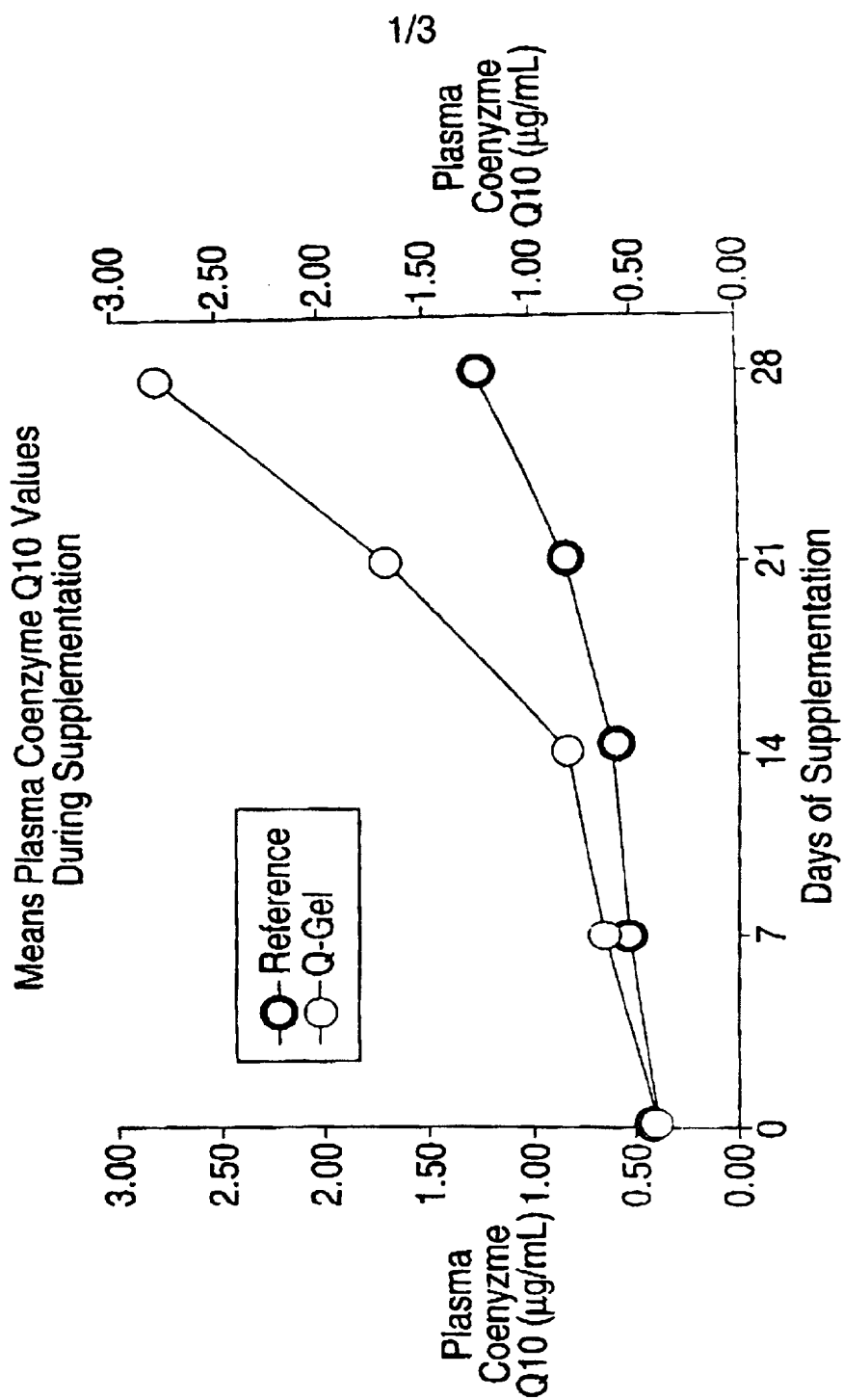


FIG. 1

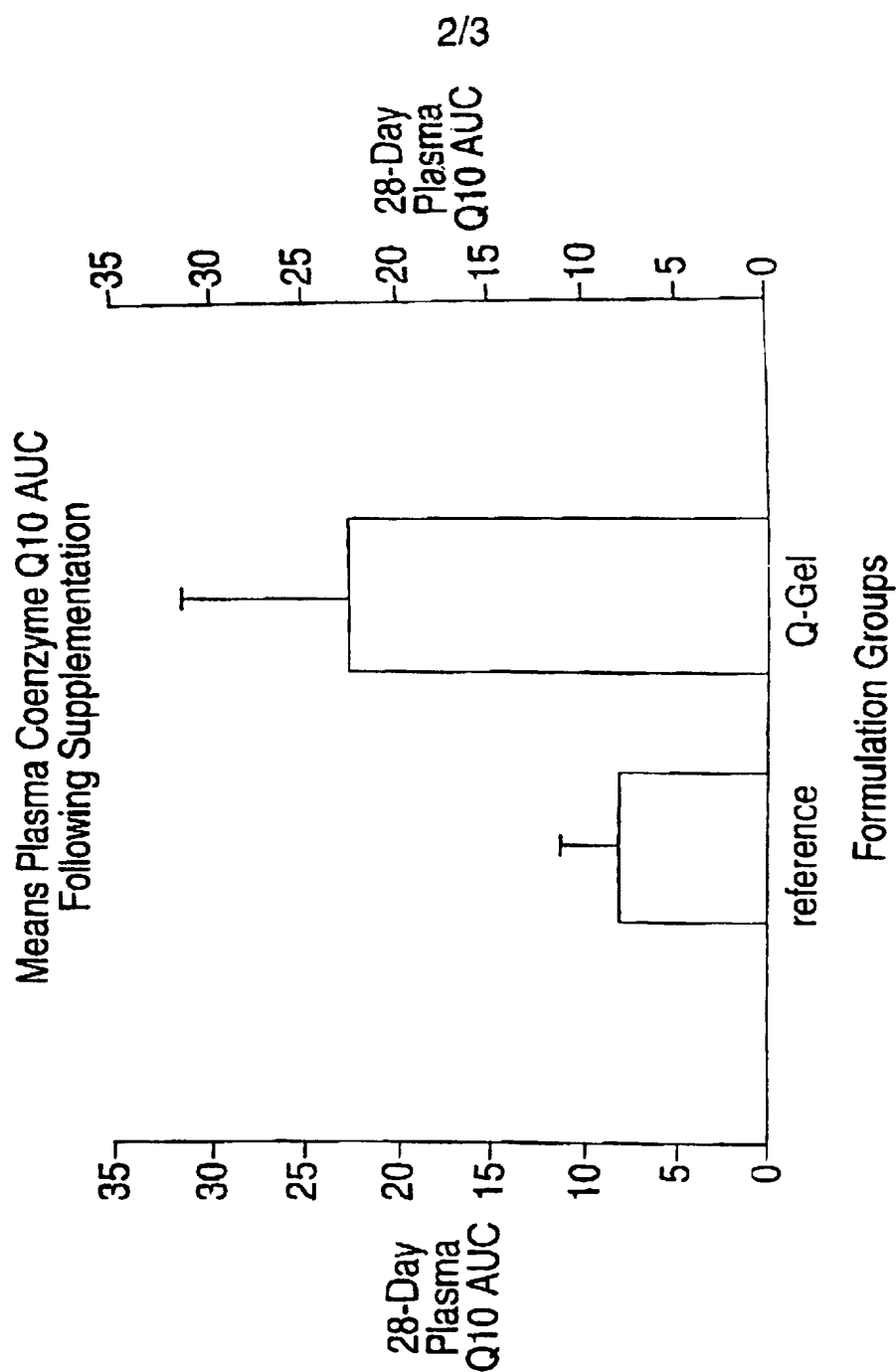


FIG. 2

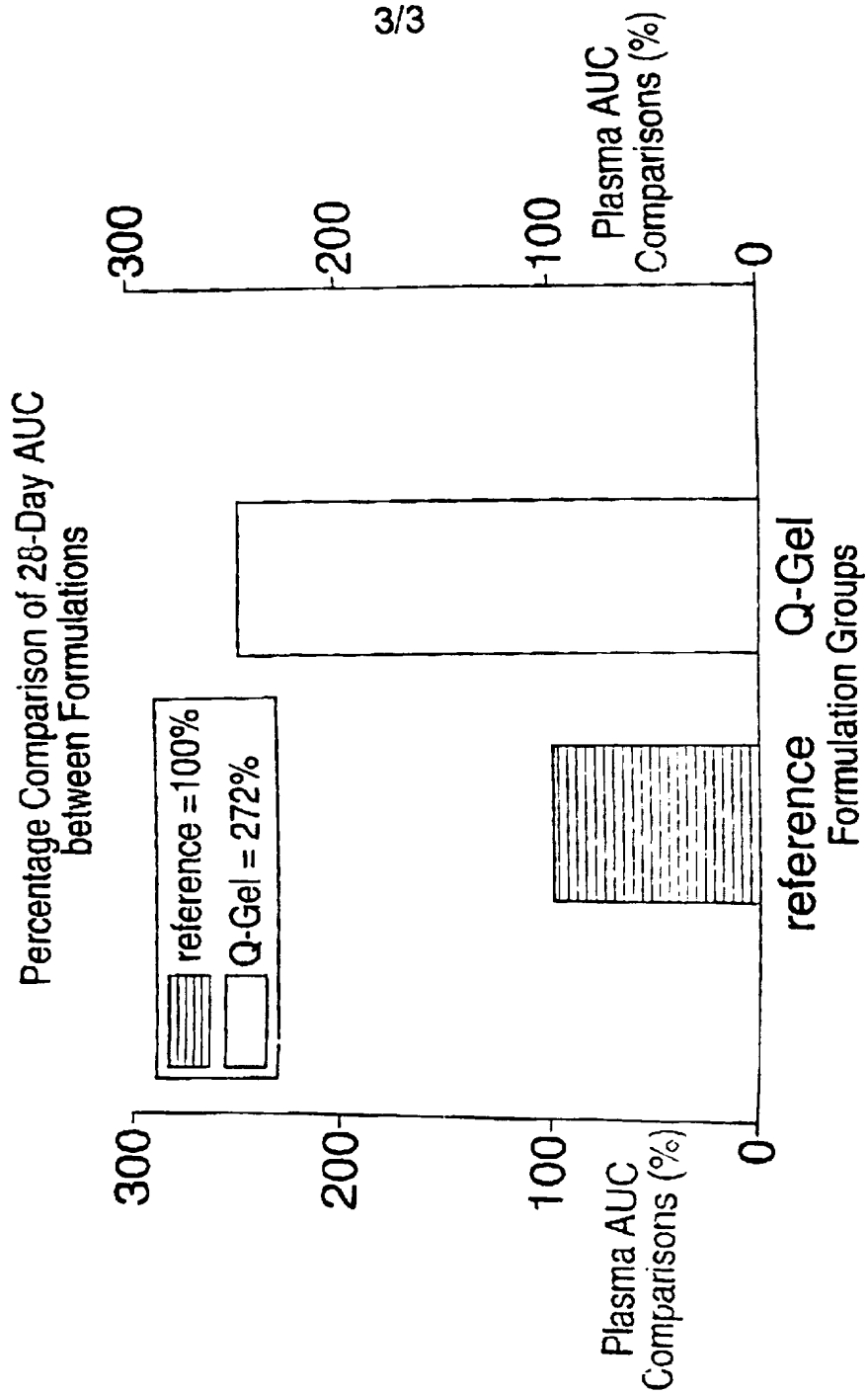


FIG. 3

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US97/12561

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC(6) : A61K 31/355 US CL : 514/458, 904, 905 According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) U.S. : 514/458, 904, 905  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched REMINGTON'S PHARMACEUTICAL SCIENCES, 18TH EDITION, MACK PUBLISHING COMPANY, 1990  Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) CAS ONLINE: span? or tween? with vitamin and glycerol or propylene glycol		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Chem. abstr., Vol. 123, 1995 (Columbus, OH, USA), the abstract No. 92898, RIBIER, A. 'Cosmetic Composition Made of an Oil in Water Emulsion Based on Oily Globules Coated with a Lamellar Liquid Crystal Coating.' EP 641557 A1 1995.	1-23
Y	Chem. abstr., Vol. 118, 1992 (Columbus, OH, USA), the abstract No. 66767, COLE, S.K. 'Studies Using a Nonionic Surfactant-Containing Drug Delivery System Designed for Hard Gelatin Capsule Compatibility.' Int. J. Pharm. 1992, 88(1-3), 211-220.	1-23
Y	Chem. abstr., Vol. 115, 1991 (Columbus, OH, USA), the abstract No. 160932, TOMKA, I. 'Encapsulation of Materials by Starch.' DE 4002257 A1 1991.	1-23
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* "A" "B" "L" "O" "P"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance earlier document published on or after the international filing date document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed	*T* *X* *Y* *G* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art document member of the same patent family
Date of the actual completion of the international search 09 OCTOBER 1997		Date of mailing of the international search report 19 DEC 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230		Authorized officer KIMBERLY JORDAN Telephone No. (703) 368-1235 <i>Collins</i>